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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/057,467

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Garry P. Nolan

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11/21/2005

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EXAMINER

SMITH, CAROLYN L

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/057,467

Applicant(s)

NOLAN, GARRY P.

Examiner

Carolyn L. Smith

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 8-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>07052005</u> . | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission, filed 6/10/05 and 7/5/05, have been entered.

Amended claims 8 and 21-23, filed 6/10/05, are acknowledged.

The information disclosure statement, filed 7/5/05, has been fully considered.

Claims herein under examination are 8-25.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 8-19, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. (US 5,763,192) in view of Rayner et al. (1994) in view of Gonda et al. (1989) and Scott et al. (1994).

The claims are drawn to a method of screening for phenotypes in cells comprising a library of retroviral vectors comprising random sequences of up to 10 amino acids in length that express peptides comprising an amino-terminal glycine. In some embodiments the random sequences are sequenced after selection and isolation, the cells are mammalian cells, the library comprises up to  $10^9$  members, and the inserts are linked to a fusion partner. In some embodiments the phenotype is cell growth or cell death.

Kauffman et al. shows in the abstract and throughout the use of libraries of expression vectors encoding random polypeptides to screen for desired phenotypes. Kauffman et al. shows in column 1 that their method may be used to select for a wide range of properties conferred by the random peptide. Kauffman et al. shows in column 2, lines 13-16 that the expression vector can be viral and the host cell can be a eukaryotic cell. Kauffman shows in column 3, lines 45-56 that beta galactosidase fusion proteins linked to the random sequence have advantages in allowing for purification of the protein. Kauffman et al. shows in column 8, lines 20-22 that the library can have up to a billion members. Kauffman et al. shows in column 12-13 selection of phenotypic properties that affect the survival of the host cell, and selection of polypeptides that catalyze a desired reaction or regulate gene expression in vivo. Kauffman et al. does not show use of retroviral vectors, use of a glycine N-terminal to the randomized insert of up to 10 amino

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acids in length, use of mammalian host cells, a method of using presentation structures in random peptide libraries, or sequencing the selected inserts.

Rayner et al. shows retroviral vector cDNA libraries in the abstract and throughout.

Rayner et al. shows on page 880 that retroviral vectors have advantages of efficiency and stable integration and expression, and allow for selection of phenotypes of infected cells. Rayner et al. show a cDNA library in their retroviral vector with  $1.5 \times 10^6$  members on page 882. Rayner et al. shows screening infected mammalian T cells for acquisition of the phenotype of granulocyte-macrophage colony-stimulating factor (GM-CSF) independence in table 2. The sequence of isolated cells with the desired phenotype was determined as shown on page 885, and resulted in confirmation that IL-3 or GM-CSF expressing retroviral library members were in the selected cells. Rayner et al. concludes on page 886 that their method has general utility for isolation of any cDNA for which a functional screen can be devised, including differentiation along pathways that are not normally shown by a particular cell type.

Gonda et al. shows in the abstract and throughout that the amino terminal amino acid of a polypeptide controls the stability of the polypeptide in mammalian reticulocytes. Gonda et al. shows that glycine is among the set of amino acids that confer the highest stability to polypeptides.

Scott et al. describe using random peptide libraries up to 10 amino acids in length (title; page 41, col. 2, last paragraph; Table 1; page 44, col. 2, second full paragraph). Scott et al. reviews random peptide libraries. Scott et al. shows the use of presentation structures to facilitate activity of the random peptide insert on page 40.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kauffman et al. by use of mammalian cells and retroviral vectors because Rayner et al. shows that retroviral vectors are advantageous to screen libraries in mammalian cells because they are efficient and stably integrated. It would have been further obvious to sequence the selected clones to further characterize the insert because Rayner et al. shows use of sequencing to characterize selected inserts. It would have been further obvious to construct the libraries of random peptides to contain an amino-terminal glycine residue because Gonda et al shows that amino-terminal glycines confer stability to polypeptides in mammalian cells. It would have been further obvious to construct libraries of random peptides of up to 10 amino acids in length because Scott et al. emphasize new approaches for such techniques in order to find ligands that serve as leads for pharmaceutical development purposes (Scott et al., abstract). It would have been further obvious to modify the vectors of Kauffman et al. in view of Rayner et al. in view of Gonda et al. by use of a presentation structure because Scott et al. shows that presentation structures help enhance the activity of random peptide inserts.

Claim 8, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. in view of Rayner et al. in view of Gonda et al. and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above, and further in view of Garcia-Bustos et al.

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The claims are drawn to a method of using a library comprising nuclear localization signal peptides fused to random peptides.

Kauffman et al. in view of Rayner et al., Gonda et al. and Scott et al., as applied to claims 8-10, 11-19, 21, and 22 above does not show a method of using a library comprising nuclear localization signal peptides fused to random peptides.

Garcia-Bustos et al. reviews nuclear localization signals. Garcia-Bustos et al. shows on pages 84-85 that fusion of a nuclear localization signal to a protein directs the protein to localize to the cellular nucleus.

Garcia-Bustos et al. state the full potential of a genetic approach in the study of nuclear import has not yet been realized (page 87, col. 1, second paragraph). Garcia-Bustos et al. state proteins are targeted to the nucleus by specific signals (NLSs) that can render a cytoplasmic protein nuclear or when deleted or mutated, no longer promote nuclear uptake of the protein in which they reside (page 88, col. 1, second full paragraph). Garcia-Bustos et al. state nuclear protein localization is subject to complicated regulatory mechanisms since the presence of certain proteins in the nucleus is required only at very specific moments in the cell cycle or only in response to short-lived stimuli (page 98, col. 1, third paragraph). Kauffman shows in column 3, lines 45-56 that beta galactosidase fusion proteins linked to the random sequence have advantages in allowing for purification of the protein. Kauffman describes proteins bound to regulatory proteins controlling transcription activity of nucleic acids (col. 4, lines 32-37). Rayner et al. mention expression cloning techniques to isolate regulatory molecules involved in regulatory pathways (abstract and page 880, col. 1, first paragraph and col. 2, first full paragraph). It would have been obvious to a person of ordinary skill in the art at the time the

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invention was made to modify the proteins of Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above by addition of a nuclear localization signal because Rayner et al. shows that retroviral vectors are advantageous to screen libraries involving regulatory proteins in a practical, efficient, and stably integrated manner. One of ordinary skill in the art would have been motivated to make this modification for identification of defective mutants involving nuclear protein localization in regulatory pathways, as stated by Garcia-Bustos et al. (page 83, first paragraph and page 87, col. 1, second paragraph and page 99, col. 1, second paragraph).

Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above, and further in view of Abbas et al.

The claims are drawn to a method of using a library of random peptides to modulate cellular differentiation. In some embodiments the differentiation markers are characteristic of T-cells or B-cells.

Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al., as applied to claims 8-10, 11-19, 21, and 22 above does not show alterations of differentiation markers that are characteristic of T cell or B cell activation.

Abbas et al. reviews T cell and B cell differentiation particularly on pages 236-239.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to extend the screening of phenotypes of Kauffman et al. in view of Rayner



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et al. in view of Gonda et al. and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above to determine states of differentiation of T cells and B cells because Abbas et al. shows that such differentiation is important in the function of the immune system, and such screening would allow researchers to gain further insights into the mechanisms of regulation of differentiation of T cells and B cells.

Applicants state they have amended the claims to include the limitation “of up to 10 amino acids in length”. Applicants summarize Kauffman et al., Rayner et al., and Gonda, stating how these references do not include the limitation. It is noted that this limitation may be found in the Scott et al. reference, such as in Table 1. Applicants argue that Rayner et al. do not describe randomized sequence of amino acids. It is noted that not all limitations in a 35 USC 103(a) rejection must come from a single reference and that motivation to combine references need not come from every single reference. Applicants argue that Rayner et al. is directing away from the claimed invention because Rayner et al.’s cDNA-encoded proteins contain a defined, ordered sequence of amino acids and is for situations where one knows that a particular protein exists and further knows how to assay for that protein. This statement is found unpersuasive as the instant claims use “comprising” language which does not exclude other defined cDNA-encoded proteins to be present. Also, the instant claims state nothing about whether a particular protein needs to be known to exist before or any knowledge or lack thereof of how to assay for a protein. Rayner et al. concludes on page 886 that their method has general utility for isolation of any cDNA (i.e. natural or synthetic) for which a functional screen can be devised, including differentiation along pathways that are not normally shown by a particular cell type.

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Applicants argue that Kauffman et al. in view of Rayner et al., Gonda, and Scott et al. do not teach a randomized amino acid sequence of up to 10 amino acids in length. It is noted that this limitation may be found in the Scott et al. reference, such as in Table 1. Applicants argue that Scott et al.'s disclosure is directed to random peptide libraries that are cell-free and contain mixtures of random peptides. It is noted that the instant claims contain "comprising" language which can include more than one randomized peptide. It is further noted that not all limitations in a 35 USC 103(a) rejection must come from a single reference.

Applicants argue that Kauffman et al. in view of Rayner et al., Gonda, and Garcia-Bustos (and newly included Scott et al.) do not teach a randomized amino acid sequence of up to 10 amino acids in length. It is noted that this limitation may be found in the Scott et al. reference (now included in each 35 USC 103(a) rejection above), such as in Table 1.

Applicants argue that Kauffman et al. in view of Rayner et al., Gonda, and Abbas (and newly included Scott et al.) do not teach a randomized amino acid sequence of up to 10 amino acids in length. It is noted that this limitation may be found in the Scott et al. reference (now included in each 35 USC 103(a) rejection above), such as in Table 1.

### ***Conclusion***

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The

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faxing of such papers must conform to the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

November 10, 2005

 11/14/05  
**ARDIN H. MARSCHEL**  
**SUPERVISORY PATENT EXAMINER**